Austin Journal of Surgery

Open Access

Austin Publishing Group

Special Article: Congenital Anomalies

Chromosomal Abnormalities Related to Infertility and Sexual Development Disorders in Boys

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Received: May 07, 2024
Accepted: June 03, 2024
Published: June 10, 2024

Abstract

Background: Infertility continues to be an important public health problem and the important role of genetic factors in the pathogenesis of infertility is increasing day by day. Despite this, the molecular and genetic factors underlying the cause of infertility remain largely undiscovered. Chromosomal Abnormalities (CAs) are the main genetic risk factor associated with infertility and Sexual Development Disorders (SDD). Therefore, karyotyping is important in the routine work of defective boys.

Objective: The aim of this study was to define the frequency of CAs among men which referred to our department due to infertility and sexual development disorders.

Materials and Methods: In this retrospective study, we investigated 302 boys which referred to our department. For chromosome analysis, heparinized peripheral blood samples were cultured, harvested and banded according to standard methods.

Results: Out of 302 boys, 214 patients (70.9%) had a normal karyotype, and 88 patients (29.1%) showed abnormal karyotype. It was determined that 47.7% of these patients were infertility, 19.3% had hypogodism, 21.6% had genital malformation, 9.1% were intersex, and 2.3% had gender mismatch. Of the abnormal CAs, 47 cases (48.9%) had Klinefelter syndrome, 17 (17%) had X and Y mosaicism (mosaic Turner syndrome), 10 had Y chromosome structural disorder, 4 (5.7%) had autosomal CAs and 2 (2.3%) of them had gender mismatch.

Conclusion: This study allows us to improve our basic knowledge of the genetic causes of male infertility. The results from this study demonstrated that it is an important cause of CAs in infertile, genital disorders, hypogonodism and intersex men. Therefore, cytogenetic analysis is necessary for the diagnosis and definitive diagnosis of the genetic disease in every man with these conditions. However, these analyzes are very useful in genetic counseling, assessment of recurrence risk, clinical treatment, and prevention of hereditary genetic diseases and disorders.

Keywords: Cytogenetics; Chromosomal aberrations; Infertility; Sexual development disorders

Introduction

The 46,XY differences of sex development can result either from decreased synthesis of testosterone and/or DHT or from impairment of androgen action. 46,XY SDD occur with the presence or absence of mullerian structures, micropenis, atypical or female external genitalia caused by incomplete intrauterine masculinization. Male gonads are identified in the majority of 46,XY SDD patients, but in some of them no gonadal tissue is found. More than 75 genes involved in gonadal development and/or sex hormone biosynthesis/action are known causes of SDDs. A pair of siblings, one XY and the other XX, who were born from a consanguineous couple and had normal female external and internal genitalia associated with gonadal agenesis, have been reported [1]. The genetic causes of infertility can be Y chromosome deletion, single gene disorder, multi-factorial causes and CAs. Chromosomal aneuploidy, structural and numerical karyotype abnormalities, and Y chromosomal microdeleti-

Citation: Demirhan O. Chromosomal Abnormalities Related to Infertility and Sexual Development Disorders in Boys. Austin J Surg. 2024; 11(2): 1322.

ons are the leading causes of infetility, pregnancy loss and developmental sex disorders in humans. Infertility is a very common health problem, affecting approximately 15-20% of couples [2] and its rate is increasing day by day. The World Health Organization has defined "infertility" as a major global health problem and reported that one in seven couples live as infertile [3].

Infertility is a multifactorial condition and may result primarily from male or female factors or a combination of both. The most common causes of infertility are "unexplained" causes. Although most of the genetic causes of male infertility are still unknown. Among them CAs are one of the most common genetic causes of infertility. Male factor infertility includes chromosome and gene abnormalities, hormonal problems, genital infections, chemical and physical agents, varicose, genito-urinary obstruction, testicular dysfunction, etc. CAs are more common in patient groups with sexual ambiguity or unexplained infertility. Structural rearrangements such as microdeletions of chromosome Y and short arm isochromosome are implicated in male infertility [4]. Translocations between Y and X can lead to abnormal phenotypes that cause sexual ambiguity or infertility [5]. The ring Y chromosome can cause a broad phenotype, such as anomalies in the genital organs, hypogonadism, oligospermia, or azoospermia, however, deletion of Xp can cause gonadal dysgenesis, infertility, or amenorrhoea, depending on the breakpoint [6-8]. A translocation between X and an autosome, when occurred in the POF1 and POF2 locus, results in ovarian disorders [8]. Structural abnormalities such as reciprocal translocations and Robertsonian translocations between autosomal chromosomes can also cause male sterility as they cause unbalanced gamete formation [9,10]. Various chromosomal abnormalities of the Y chromosome can cause infertility, so genetic screening should be offered to infertile patients. Therefore, in this study, we tried to determine the frequency and types of CAs in boys with infertility and SDDs in Turkey.

Materıals and Methods

This is a retrospective study, performed at Çukurova University Medical Center, Department of Medical Biology and Genetics, Turkey. In this study, cytogenetic analyses were performed on a population of 302 patients with infertility and gender anomalies who were referred to our clinic for investigation. The age of the analyzed population ranged between 27 days-23 years, and the average age was 11.4 years. These patients were referred mostly with various clinical information such as infertility, genital disorders, hypogonodism, intersex and phenotypic gender mismatch (Table 1). None of them had environmental exposure, radiation exposure, or prescription drug usage that could account for their infertility. Informed consent was taken from the patients and donors prior to collection of heparinised blood samples. Chromosome investigations were performed on cultures of peripheral blood lymphocytes using standard techniques. In all the cases studied, at least 20 metaphases were selected and analyzed. In the case of mosaicism, 50 cells were analyzed by G-banding. CAs have been reported in accordance with the current international standard nomenclature 2016.

Table 1: Distribution of patients with chromosomal anomalies according to their clinical information.

Number of patients		%	
Normal Karyotype's	214	70.9	
Abnormal Karyotypes	88	29.1	
Total	**302**	**100**	
Clinical informations	Number of patients	Freq. in all cases(%)	Freq. in all anom(%)
Infertility	42	13.9	47.7
Hypogonadism	17	5.6	19.3
Genital malformations	19	6.3	21.6
(ambiguous, genitalia, micropenis, cryptorchidism, hypospadias)			
Intersex	8	2.6	9.1
Sex reversal	2	0.7	2.3

Statistical Analysis

The results of the two groups were compared using the two-tailed Fisher's exact test and calculated with GraphPad Software.

Results

The distribution of patients with chromosomal anomalies according to their clinical information is shown in Table 1. According to this; Of the 302 patients referred, 70.9% (214 cases) were reported to have a normal karyotype and 29.1% (88 cases) to have an abnormal chromosome setup. Considering the distribution of 88 patients with chromosome damage according to their clinical findings; 13.9% (42 cases) were infertile, 6.3% (19cases) genital disorders, 5.6% (17 cases) hypogonodism, 2.6% (8 cases) intersex and 0.7% (2 cases) genotpic gender and phenotypic gender were inconsistent.

The karyotype classification of all patients with CAs is shown in Table 2. It was found that 75.0% of all anomalies were numerical and 25.0% were structural anomalies. The most common numerical anomaly among the cases was Klinefelter karyotype

Table 2: Classification of chromosomal anomalies in infertile men with abnormal karyotype.

Abnormal Karyotypes (88 cases)	Freq. in all cases (%)	Freq. in all anom (%)
47,XXY x30	9.9	34.1
48,XXXY	0.3	1.1
48,XXYY	0.3	1.1
46,XY/47XXY x5	1.7	5.7
47,Xi(Xq)Y x3	1.0	3.4
46,XY/46,X /47,XXY x2	0.7	2.3
46,XY/46,XX/47,XXY x4	1.3	4.5
46,XY/47,XXY,del(13q22)	0.3	1.1
Total	**15.6**	**53.4**
46,XY/45,X x11	3.6	12.5
46,XY/46,XX x4	1.3	4.5
46,XY/46,XX/45,X	0.3	1.1
46,XY/46,XX/46,Xi(Xp)	0.3	1.1
Total	**5.6**	**19.3**
46,XY,Yq+ x4	1.3	4.5
46,X,del(Yq11) x3	1.0	3.4
46,XY,del(Yq),t(9;22)(q34;q1)	0.7	2.3
45,X,t(3;Y)(p11;p11)	0.3	1.1
46,XY,inv(Y)(q12;q11)	0.3	1.1
Total	**3.3**	**11.4**
46,XY,inv(9)(p11;q12) or (p12;q13) x10	3.3	11.4
46,XY,inv(5),del(12p13)	0.3	1.1
46,XY,robt(14;15)	0.3	1.1
46,XY, anop(%15)	0.3	1.1
Total	**4.3**	**14.8**
46,XX males (sex revelsal) x2 **Total**	**0.7**	**2.3**

(KS, 47,XXY, 47 cases). KS karyotype was found in 15.6% of all cases and 53.4% among all anomaly. Klinefelter karyotype in itself 63.8% classical KS (30 cases) (47,XXY), 25.5% mosaic (12 cases) (46,XY/47XXY), 6.4% structural (3 cases) [47,Xi(Xq)Y] and 4.3% were other rare KS (2 cases)(48,XXXY, 48,XXYY). The karyotype classification of all patients with CAs is shown in Table 2. It was found that 75.0% of all anomalies were numerical and 25.0% were structural anomalies. The most common numerical anomaly among the cases was Klinefelter karyotype (KS, 47,XXY, 47 cases). KS karyotype was found in 15.6% of all cases and 53.4% among all anomaly. Klinefelter karyotype in itself 63.8% classical KS (30 cases) (47,XXY), 25.5% mosaic (12 cases) (46,XY/47XXY), 6.4% structural (3 cases) [47,Xi (Xq)Y] and 4.3% were other rare KS (2 cases) (48,XXXY, 48,XXYY). We found that 5.6% of all cases and 19.3% of all anomalies were sex chromosome mismatch, that is, individuals with both XX and XY cell lines. The frequency of Y chromosome structural rearrangements (Yq and Yq) was 3.3% and 11.4% (in 0 cases) among all cases and all anomalies, respectively. Y chromosome structural anomalies include; It was reported that four of them have long arm increase (Yq+), four have long arm deletion (Yq-) (one of which is an autosomal translocation carrier), one has long inversion (Yq) and one has a translocation between chromosome 3 and Y. The frequency of autosomal CAs detected in the present study was 6.0% and 20.1% (18/302 and 88 patients), respectively, among all cases and anomalies; consisting of a patient with 46,XY/47,XXY,del(13q22), one with 46,XY,del(Yq),t(9;22)(q34;q1), one with 45,X,t(3;Y)(p11;p11), eleven with 46,XY,inv(9)(p11;q12) or (p12;q13), one with 46,XY,inv(5),del(12p13), one with 46,XY,robt(14;15), one with 46,XY, anop(%15) and one with 46,XY,21s++. Two cases showed sex reversal with the 46,XX karyotype; were 0.7% and 2.3% among all cases and all anomalies, respectively.

Discussion

Although the genetic basis underlying sexual development disorders and infertility is largely unknown, numerical and structural CAs play a major role in these disorders. Genetic causes include Y and X chromosome deletions, single gene disorders, chromosomal aneuploidies, structural and numerical CAs, and multifactorial causes. Numerical and structural CAs played a principal role in male infertility. Chromosomal aneuploidies are the leading cause of pregnancy loss and developmental disorders, and men with numerical or structural karyotype abnormalities may also produce aneuploid sperm. Gonosomal aneuploidies (X and Y) are the leading cause of pregnancy loss and developmental disabilities in humans, such as Klinefelter syndrome (47,XXY) are the most frequent CA in infertile men. We also reported the most common gonosomal aneuploidies (XXY) in patients boys. In this study, gonosomal aneuploidy (Klinefelter syndrome) was found to be 15.6% among all cases and 53.4% among all anomalies. Classical karyotype (47,XXY) was found to be 63.8% in children with KS. This is followed by mosaics (46,XY/47,XXY, 14.8%), isochromosome X (47,Xi(Xq), 3.4%), rare X and Y aneuploidies (48,XXXY and 48,XXYY, 2.3%) and others [46,XY/47,XXY,del(13q22), 1.1%]. In a similar study, it was also reported that approximately 80% of KS patients had 47,XXY karyotype, and 20% of other sex-chromosome numerical abnormalities (48,XXXY, 48,XXYY, 49,XXXXY), mosaics and structural sex chromosome damages (11). The extra X chromosome is sporadically due to the failure of gametogenesis to separate during the first or second meiotic division or due to mitotic segregation in the developing zygote. Boys with 47,XXY have variable phenotypic characteristics. Most cases showed the classic, well-defined phenotype, while others had various sexual behavior problems, mental retardation and developmental delay. Infertility, hypogonadism and similar complaints were also recorded in our cases. The cases with classic KS (47,XXY) or mosaic variants have severely impaired spermatogenesis, typically small and firm testicles with hyalinization of the seminiferous tubules and consequent spermatogenic failure.

Chromosomal defects were found to be twice as high in infertile men as compared to controls [12]. It has been found that at least 5% of azoospermic men have 47,XXY aneuploidy [13]. These cytogenetic damages affect semen quality and cause varying degrees of male infertility. Testicular atrophy and decreased sperm count in patients with KS can theoretically be attributed to atresia of germ cells caused by the extra X chromosome [14,15]. The classic form of KS accounts for around 11% of azoospermic individuals, whereas mosaic individuals often present with oligozoospermia [16]. Other Klienfelter mosaic types are seen in azoospermic and oligozoospermic men [17]. Testicular atrophy and decreased sperm count in patients with KS can theoretically be attributed to atresia of germ cells caused by the extra X chromosome [14,15]. Mosaic sex chromosome karyotypes are common and many combinations are possible. We found mosaic karyotypes related to X chromosome increase in 25.5% of KS cases and 4.0% of all cases. At the same time, there were 4.3% of individuals in the KS group who had 47,XXY karyotype as well as less frequently one or two additional X and/or Y chromosomes (48,XXYY and 48,XXXY). It can be said that the high incidence of mosaic sex chromosomal aneuploidies in our patient group is associated with infertility and other clinical symptoms. With this, various mosaic patterns constitute approximately 15% of patients, the most common being 46,XY/47,XXY and the remainder are increases of the X chromosome (48,XXXY or 49,XXXXY). X-chromosome polysomies, isochromosome Xqi(Xq) or X-Y translocations, which are rare, are encountered in 0.3-0.9% of men with KS [18,19]. In the current study, structural irregularity in the form of the long arm isomer of the X chromosome [i(Xq)] was detected in three (6.4%) of the KS cases and 1% of all cases. It has been shown by observations on other structural anomalies of X chromosomes that the presence of additional material of Xq causes azoospermia and hormonal imbalance in males [20]. In general, those with ovarian failure have breakpoints within the Xq13-q26 region.

At the same time, besides the 47,XXY karyotype, a less frequent group of KS patients have additional X and/or Y chromosomes and show karyotypes like 48,XXYY, 48,XXXY or 49,XXXXY. 4.3% of our KS cases had 48,XXXY and 48,XXYY variants. The strongest known genetic marker for infertility in some men is the Y chromosome. The Y chromosome contains genes necessary for gonadal differentiation into a testis and genes for complete spermatogenesis. With this, extra copies of genes from the pseudoautosomal region of the extra X and Y chromosome contribute to the signs and symptoms of 48,XXYY syndrome. At the same time, the presence of the X chromosome results not only in spermatogenic and androgenic failure, but also in gynecomastia, expression language difficulties, higher mortality from breast cancer and non-Hodgkin lymphoma, and a higher incidence of extragonadal germ cell tumors [21-23]. There is a large amount of phenotypic variability among 46,XX/46,XY mosaic individuals. The spectrum of sexual development in these mosaic individuals ranges from typical sexual development to various. It is possible that a large percentage of XX/XY mosaics are phenotypically male or female. We found that 5.6% of all cases and 19.3% of all anomalies were sex chromosome mismatch, that is, individuals with both XX and XY cell lines. The-

se cases had congenital irregularities including incomplete intrauterine masculinization, micropenis or atypical development of gonadal or anatomical sex, such as female external genitalia. Sex chromosome mismatch refers to individuals with both XX and XY cell lines. This mix of sex chromosomes can be explained by three genetic mechanisms; 46,XX/46,XY may be mosaic-based, most commonly by in utero combination of two fertilized zygotes, or cells may be fertilized by an X and a Y sperm, respectively [24,25]. Patients with mixed gonadal dysgenesis have a broad phenotypic spectrum including normal women or women affected with Turner's syndrome, men with hypospadias, and male or female pseudohermaphrodism. Pseudohermaphrodite describes individuals whose gonadal sex is compatible with chromosomal structures but with atypical development of external genitalia. The 46,XY differences in sex development may result from either decreased testosterone and/or DHT synthesis or impaired androgen effect. DSD is characterized by micropenis, atypical or female external genitalia caused by incomplete intrauterine masculinization in the presence or absence of Müllerian structures. Most 46,XY DSD-patients have male gonads, but some lack gonadal tissue. Complete absence of virilization results in normal female external genitalia. These patients usually seek medical attention at puberty because of the absence of breast development and/or primary amenorrhea. The presence of both testicular and ovarian tissue (ovotesticular disorder) has been reported in 46,XX/46,XY mosaic cases [26]. 46,XX/46,XY individuals have one or more irregularities such as a small phallus midway in size between the clitoris and penis, an incompletely closed urogenital opening, and an abnormal urethral opening on the perineum. Although some people with 46,XX/46,XY have ovarian tissue and testicular tissue at the same time, both gonads are not functional. A mix of male and female traits may emerge at puberty.

Structural CAs are an important cause of miscarriage, infertility, congenital anomalies and mental retardation in humans. The frequency of Y chromosome structural rearrangements was also found to be higher than the frequency observed in newborn series. Some cases of Y chromosome structural rearrangements are known as a result of failure of pairing between X and Y chromosomes. We found deletions in the long arm (q11, q12) of the Y chromosome in four (1.3%) of our cases. Deletion of the Y chromosome region containing the azoospermia factor is considered the most common genetic cause of male infertility. The Y chromosome contains several genes required for spermatogenesis and loss of one or more of such genes can cause impairment of this process. The long arm of the Y chromosome contains many sequences that predispose it to self-recombination during spermatogenesis, thus making it susceptible to intrachromosomal deletions. Such deletions lead to copy number variation that leads to male sterility. In individuals with gonadal dysgenesis that bear a full or even partial fragments of Y chromosome have a high risk of developing gonadal tumours specifically gonadoblastoma [27-29]. Other karyotype abnormalities Infertile men can have other Y chromosome abnormalities including mosaicism, ring Y, deletion Y, and isodicentric Y. Deletion is a type of mutation involving the loss of genetic material. The Y chromosome contains several genes required for spermatogenesis and loss of one or more of such genes can cause impairment of this process. After the Klinfeleter syndrome, Y chromosome micodeletion are the second most frequent genetic cause of infertility. Three regions on the long arm of the Y chromosome (AZFa, AZFb and AZFc) are known to be deleted in men with severe spermatogenic deficiency. The frequency of these microdeletions in azoospermic and severely oligospermic men is between 1% and 50% [30,31]. Patients with deletion Y chromosomes should undergo AZF microdeletion assays to determine if these regions are present.

We found that the long arm of the Y chromosome was longer than normal in four cases (1.3%). Few reports on male infertility have mentioned chromosomal polymorphisms or variants. These minor CAs are considered to have no clinical impact. One study reported that the increased long arm (Yq+) polymorphism of the Y chromosome was 4.4% [31] Whether chromosomal variants may alter the carrier's fertility is still an open question, as is the role of heterochromatin in meiosis. We reported that the Y chromosome was translocated to chromosome 3 in one case. Thus, a previous study revealed the cytogenetic effects on patients with infertility in a Turkish population, and the 1qh+, 16qh+, Yqh+ and inv(9) polymorphisms had frequencies of 0.5%, 1.5%, 1.82% and 0.5% respectively [32]. In addition, it has been reported that Yq+ may be associated with the risk of unexplained recurrent miscarriages and may play an important role in the development of these abortions [33]. All these findings indicate that Yq+ may be associated with the risk of the risk of infertility or SDD, may act an important role in the developm ent of these diseases.

Other chromosome damages that can cause infertility can include translocations and inversions. It is now known that some reciprocal translocations are associated with failure or disruption in sperm production. It has been reported that approximately seven times more Robertsonian heterozygotes are present in infertile couples [34]. Robertsonian and reciprocal translocations are found more commonly in the oligospermic than the azoospermic population [35]. In addition to X and Y chromosomes, some autosomal genes also play a role in determining sex [36]. Autosomal CAs are relatively common in humans. These may be numerical and structural CAs. These abnormalities are known to be associated with infertility, increased pregnancy loss, and birth of disabled children. The frequency of autosomal CAs in infertile men ranges from 3% to 19%: 3% in mild infertility cases and 19% in men with non-obstructive azoospermia [37].

We found inversion type autosomal and gonosomal structural irregularities in twelve (4.0%) of our cases. Chromosomal inversions can also cause infertility, spontaneous abortions and birth defects. Because inversions produce somewhat unstable gametes, they can interfere with sperm count and fertility. Studies on unbalanced gametes in balanced inversion carriers have been scarce, although few studies have reported unbalanced sperm ranges between 1% and 54% [38,39]. Pericentric inversions of the Y chromosome are quite common, with most cases being familial, with an estimated incidence in males of 0.6-1:1,000 in the general population. We also detected paracentric inversion Y in one case. Although it is known that the risk of mental retardation or miscarriage is not significantly increased in pericentric inversion Y carriers and there are no abnormal phenotypic features, this chromosomal damage should still be considered. Inversions are risky for the offspring and not the carriers, a carrier of either type of inversion is at risk of producing abnormal gametes. On the other side, pericentric inversions of chromosome 9 are a common occurrence. Most of the observed inv(9)s are not believed to cause any specific phenotypic abnormality. However, some studies have been associated with phenotypic disorders. Carriers of large pericentric inversions are at risk for meiotic recombination within the

inverted segment, resulting in duplication or deletion of chromosomes in the gametes. If crossing-over occurs, unbalanced or abnormal gametes may result. Gametes with the unbalanced inversion may cause spontaneous fetal death and malformed offspring. Many studies have reported that inv(9) was closely associated with recurrent spontaneous miscarriage, infertility, congenital anomalies, and idiopathic reproductive failure [40-42]. As a matter of fact, we noted that in our cases, there were complaints of infertiliy, SDD and abnormal clinical conditions. All these findings show that inv(9) is not as harmless as it seems. Although the breakpoints of our cases were different, we think that the chromosomes have a high tendency to be exposed to inversion. We detected inv(9) in 10 cases (3.3% among all cases and 11.4% among all anomalies). The most widely recognized inversion is 46,XY,inv(9)(p11;q13) in oligozoospermic infertile male. Inversion of chromosome nine could be acknowledged as a reason of fertility problems. Similarly, 46,Y,inv(X)(q12;q25) inversion has been reported in an infertile man with a Klinefelter-like phenotype. On the other hand, pericentric inversion of chromosomes 1, 3, 5, 6 and 10 is related to abnormal sperm production in infertile men.

Loss of the short arms of acrocentric chromosomes does not have phenotypic consequences, because the lost sections do not contain unique genetic sequences. However, unbalanced gametes of heterozygous carriers are common and give rise to a monosomic or trisomic fetus. Most monosomies and trisomies are lethal and spontaneously abort early in the pregnancy. We found autosome-autosome translocation [14,15] in one case. Autosome-autosome translocations cause decreased fertility and the translocated chromosomes to synapse in meiosis. The most common Robertsonian translocation observed in infertile males is t(13q14q). t(13q14q) and t(14:21) revealed abnormal behavior of autosomes rearranged in meiosis causing infertility during spermatogenesis in infertile carriers [43]. All this information confirms that the autosomal translocation we found in our case may cause infertility and and genital disorders.

Conclusion

The rates of chromosomal abnormalities in children with suspected chromosomal disorders were shown. This study concludes that chromosomal defects are significantly associated with infertility and genital disorders. Moreover, this study needs to be confirmed with further investigations the role of chromosomal aberrations in the etiology of infertility and genital ambiguity. The chromosomal analysis is an important investigation in male with infertility and genital ambiguity. Therefore, it is recommend that for better counselling, chromosomal analysis should be done in all cases of infertility and suspected abnormalities. In the remaining patients where no chromosomal abnormality can be detected, other possible causes of defects e.g. single gene defect, multifactorial or environmental factors need to be probed in order to find possible management strategies.

References

1. Mendonca BB, Barbosa AS, Arnhold IJ, McElreavey K, Fellous M, Moreira-Filho CA. Gonadal agenesis in XX and XY sisters: evidence for the involvement of an autosomal gene. Am J Med Genet. 1994; 52: 39-43.
2. Mitta A, Yadav S, Yadav SS, Bhardwaj A, Kaur R, Singh P, et al. An epidemiological study of infertility among urban population of Ambala, Haryana. Int J Interdiscip Multidiscip Stud. 2015; 2: 124-30.
3. Greenhall E, Vessay M. The prevalence of subfertility: our view of the current confusion and a report of two new studies. Fertil Steril. 1990; 54: 978-983.
4. Akbari MT, Kachoui MA, Pourmand GR, Behjati F, Asbagh FA. Cytogenetic abnormalities in 222 infertile men with azoospermia and oligospermia in Iran: report and review. Indian Journal of Human Genetics. 2012; 18: 198-203.
5. Ravel C, Siffroi JP, Y chromosome structural abnormalities and Turner's syndrome. Gynécologie, Obstétrique & Fertilité. 2009; 37: 511-518.
6. Wolff DJ, Miller AP, Van Dyke DL, Schwartz S, Willard HF. Molecular definition of breakpoints associated with human Xq isochromosomes: implications for mechanisms of formation. Am J Hum Gen. 1996; 58: 154-160.
7. Simpson JL, Rajkovic A. Ovarian differentiation and gonadal failure. Am J Med Gen. 1999; 89: 186-200.
8. Goswami D, Conway GS. Premature ovarian failure. Hum Rep Update. 2005; 11: 391-410.
9. Martin RH. Cytogenetic determinants of male fertility. Human Reproduction Update. 2008; 14: 379-390.
10. Morin SJ, Eccles J, Iturriaga A, Zimmerman RS. Translocations, inversions and other chromosome rearrangements. Fertility and Sterility. 2017; 107: 19-26.
11. Lanfranco F, Kamischke A, Zitzmann M, Nieschlag E. Klinefelter's syndrome. Lancet. 2004; 364: 273-283.
12. Katagiri Y, Neri QV, Kent-First M, Wang A, Rosenwaks Z, Palermo GD. Chromosomal status of infertile couples and the offspring created by ICSI. Fertil Steril. 2002; 78: S16-S16.
13. Amol ZD, Gangane SD, Rakhi MM, Swati AD. Cytogenetic study in male infertility. IOSR. J Dent Med Sci. 2013; 5: 5-11.
14. Burgoyne PS. The role of the sex chromosomes in mammalian germ cell differentiation. Ann Biol Anim Biochim Biophys. 1978; 18: 317-325.
15. Elfateh FR, Zhang WZ, Jiang Y, Chen S, Liu R. Influence of genetic abnormalities on semen quality and male fertility: A four-year prospective study. Iran J Reprod Med. 2014; 12: 95-102.
16. van Assche E, Bonduelle M, Tournaye H, Joris H, Verheyen G, et al. Cytogenetics of infertile men. Hum Reprod. 1996; 11: 1-24.
17. De-Braekeleer M, Dao TN. Cytogenetic studies in male infertility: a review. Hum Reprod. 1991; 6: 245-250.
18. Arps S, Koske-Westphal T, Meinecke P, Meschede D, Nieschlag E, Harpecht W, et al. Isochromosome Xq in Klinefelter syndrome: report of 7 new cases. Am J Med Genet. 1996; 64: 580-582.
19. Kalousek D, Biddle CJ, Rudner M, Arronet GH, Fraser FC. 47,X,i(Xq),Y karyotype in Klinefelter's syndrome. Hum Genet. 1978; 43:107-110.
20. Fryns JP. Klinefelter syndrome and the Xqll-22 region. Clin Genet. 1982; 20: 237.
21. Groth KA, Skakkebaek A, Host C, Gravholt CH, Bojesen A. Clinical review: Klinefelter syndrome–a clinical update. J Clin Endocrinol Metab. 2013; 98: 20-30.
22. Swerdlow AJ, Schoemaker MJ, Higgins CD, Wright AF, Jacobs A, et al. Cancer incidence and mortality in men with Klinefelter syndrome: a cohort study. J Natl Cancer Inst. 2005; 97: 1204-10.
23. Aguirre D, Nieto K, Lazos M, Pena YR, Palma I, Kofman-Alfaro S, et al. Extragonadal germ cell tumors are often associated with Klinefelter syndrome. Hum Pathol. 2006; 37: 477-80.

24. Niu DM, Pan CC, Lin CY, Hwang BT, Chung MY. Mosaic or chimera? Revisits an old hypothesis about the cause of 46,XX/46,XY hermaphrodite. J Pediatr. 2002; 140: 732-735.

25. Chen CP, Chern SR, Sheu JC, Lin SP, Hsu CY, Chang TY, et al. Antenatal diagnosis, sonographic findings, and molecular genetic analysis of a 46,XX/46,XY true hermaphrodite chimera. Prenate Diagn. 2005; 25: 502-506.

26. Dreger AD, Chase C, Sousa A, Gruppuso PA, Frader J. Changing the terminology/taxonomy for intersex: a scientific and clinical rationale. J Pediatr Endocrinol Metab. 2005; 18: 729-733.

27. Jørgensen A, Johansen ML, Juul A, Skakkebaek NE, Main KM, Rajpert-De Meyts E. Pathogenesis of germ cell neoplasia in testicular dysgenesis and disorders of sex development. Semin Cell Dev Biol. 2015; 45: 124-37.

28. Kido T, Lau YF. Roles of the Y chromosome genes in human cancers. Asian J Androl. 2015; 17: 373-380.

29. Huang H, Wang C, Tian Q. Gonadal tumour risk in 292 phenotypic female patients with disorders of sex development containing Y chromosome or Y-derived sequence. Clin Endocrinol. 2017; 86: 621-7.

30. Foresta C, Ferlin A, Garolla A, Moro E, Pistorello M, Barbaux S, et al. High frequency of well-defined Y-chromosome deletions in idiopathic Sertoli cell-only syndrome. Hum Reprod. 1998; 13: 302-07.

31. van der Ven K, Montag M, Peschka B, Leygraaf J, Schwanitz G, Haidl G, et al. Combined cytogenetic and Y chromosome microdeletion screening in males undergoing intracytoplasmic sperm injection. Mol Hum Reprod. 1997; 3: 699-704.

32. Abramsson L, Beckman G, Duchek M, Nordenson I. Chromosomal aberrations and male infertility. J Urol. 1982; 128: 52-3.

33. Ahmet OC, Isilay O, Fatma D, Munis D. Cytogenetic results of patients with infertility in middle anatolia, turkey: do heterochromatin polymorphisms affect fertility?. J Reprod Infertil. 2010; 11: 179-181.

34. Yan Wang, Gang Li, Man-Zhen Zuo, Jun-Hua Fang, Hai-Rong Li, Dan-Dan Quan, et al. Y chromosome polymorphisms may contribute to an increased risk of male-induced unexplained recurrent miscarriage. Biosci Rep. 2017; 37: BSR20160528.

35. Tharapel AT, Tharapel SA, Bannerman RM. Recurrent pregnancy losses and parental chromosome abnormalities: a review. Br J Obstet Gynaecol. 1985; 92: 899-914.

36. Mau-Holzmann UA. Somatic chromosomal abnormalities in infertile men and women. Cytogenet Genome Res. 2005; 111: 317-36.

37. Wijchers PJ, Yandim C, Panousopoulou E, Ahmad M, Harker N, Saveliev A, et al. Sexual dimorphism in mammalian autosomal gene regulation is determined not only by Sry but by sex chromosome complement as well. Dev Cell. 2010; 19: 477-84.

38. Yoshida A, Kazukiyo M, Masafumi S. Cytogenetic survey of 1,007 males. Urol Int. 1997; 58: 166-176.

39. Mikhaail-Philips MM, McGillivray BC, Hamilton SJ, Ko E, Chernos J, Rademaker A, et al. Unusual segregation products in sperm from a pericentric inversion 17 heterozygote. Hum Genet. 2005; 117: 357-65.

40. Yakut T, Acar H, Egeli U, Kimya Y. Frequency of recombinant and nonrecombinant products of pericentric inversion of chromosome 1 in sperm nuclei of carrier: by FISH technique. Mol Reprod Dev. 2003; 66: 67-71.

41. Elkarhat Z, Kindil Z, Zarouf L, Razoki L, Aboulfaraj J, Elbakay C, et al. Chromosomal abnormalities in couples with recurrent spontaneous miscarriage: a 21-year retrospective study, a report of a novel insertion, and a literature review. J Assist Reprod Genet. 2019; 36: 499-507.

42. Jeong SY, Kim BY, Yu JE. De novo pericentric inversion of chromosome 9 in congenital anomaly. Yonsei Med J. 2010; 51: 775-780.

43. Demirhan O, Pazarbasi A, Suleymanova-Karahan D, Tanriverdi N, Kilinc Y. Correlation of clinical phenotype with a pericentric inversion of chromosome 9 and genetic counseling. Saudi Med J. 2008; 29: 946-51.

44. Shah K, Sivapalan G, Gibbons N, Tempest H, Griffin DK. The genetic basis of infertility. Hum Reprod. 2003; 126: 13-25.